

A 62-year-old woman with 3 episodes of anaphylaxis

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CHIEF COMPLAINT

Three episodes of anaphylaxis.

HISTORY OF PRESENT ILLNESS

A 62-year-old Hispanic woman with a history of renal cell cancer experienced her first episode of anaphylaxis during surgery in May 2002. Her systolic blood pressure dropped to 60 mm Hg several minutes after the initial incision was made in an attempted nephrectomy for her localized renal cell cancer. No hives were noted. Surgery was stopped, and the patient recovered in the intensive care unit after several doses of epinephrine and dexamethasone. She had received rocuronium and ciprofloxacin during the surgery, which were thought to be the most likely causes of the anaphylaxis. A second attempt at surgery 1 week later resulted in her second episode of anaphylaxis, again marked by a decrease in her blood pressure. This time she was not given ciprofloxacin, and the rocuronium was replaced with cisatracurium. The surgeons completed the procedure with the aid of epinephrine and dexamethasone, and the patient recovered without further incident. Three months later the patient had a third episode of anaphylaxis unrelated to surgery and was sent to the Northwestern University Allergy-Immunology Division for evaluation.

QUESTIONS

1. At this point in her history, what are the most likely causes for this patient's episodes of intraoperative anaphylaxis?

Allergic evaluation after an episode of intraoperative anaphylaxis proves challenging. This challenge begins in the operating room, where making an initial diagnosis of anaphylaxis is complicated by patients who are draped and unable to provide the classic verbal history of throat closing, shortness of breath, and pruritus that often characterize such an episode. The hives that often accompany anaphylaxis may

be not only hidden by the patient's drapes but also absent, as can be the case in severe hypotensive anaphylactic reactions. When a surgical team suspects an anaphylactic or anaphylactoid reaction as the reason for a patient's hypotension or desaturation, the instigating cause may be obscured by the multiple medications patients typically receive during anesthesia.

It has been reported that the most frequent cause of anaphylaxis during surgery is a neuromuscular blocking agent (61% to 69%), such as the rocuronium and cisatracurium used in this patient's procedures.¹ Latex has been reported to cause between 12% and 16% of cases, followed by antibiotics (8%), hypnotics (5%), colloids (3%), opioids (2.7%), and other miscellaneous culprits (2.6%).^{1,2} The literature therefore justifies the surgeon's initial suspicion of rocuronium as the most likely cause of the patient's anaphylaxis.

Given the significant cross-reactivity among muscle relaxants via their quaternary ammonium group, estimated to be as high as 84% in one report, it would also be reasonable to think that the second episode of anaphylaxis was caused by the replacement muscle relaxant cisatracurium.³ These quaternary ammonium ions have been shown to be the primary allergenic component of the muscle relaxants and have been suggested to be the primary sensitizers in patients who react on first exposure to a muscle relaxant, since these ions are widely present in our environment in drugs, cosmetics, and industrial materials.⁴ Although patient risk factors for muscle relaxant-induced anaphylaxis include previous exposure or reaction to a muscle relaxant and possibly a history of atopy or drug allergy, a significant percentage of patients without these characteristics still react on initial exposure.^{5,6} A portion of these reactions may result from prior sensitization via environmental ammonium ions as mentioned herein, but others may be explained by an anaphylactoid mechanism of mast cell activation. Although it is often difficult to determine the specific cause of an intraoperative anaphylactoid reaction and despite our lack of knowledge about how often muscle relaxants may be responsible for such anaphylactoid reactions, up to half of all episodes of intraoperative anaphylaxis may be nonimmunologic in nature.⁶

After muscle relaxants, latex allergy would be the next most likely explanation for the patient's episodes of intraop-

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erative anaphylaxis. Patients who are at high risk for the development of a natural rubber latex sensitivity include those with a history of congenital spinal cord abnormality, such as spina bifida, multiple surgical procedures, multiple catheterizations, atopy, working in the health care or rubber industry, and food allergy.⁷ As will become apparent, this patient displayed none of these risk factors, explaining why empiric latex precautions were not instituted.

Additional History

Three months after her release from the hospital, the patient experienced her third episode of anaphylaxis while eating a peach. Within minutes of ingestion, she experienced nausea; vomiting; pruritus of the mouth, face, and hands; facial swelling; and lightheadedness. She did not have urticaria but developed erythema on her hands, feet, and face. Her companion took her to the emergency department, where she was again treated successfully with epinephrine and steroids. One month later she presented for an allergic evaluation.

Current Medications

The patient's medications on presentation to the allergy clinic included hydroxyzine, 20 mg orally once before bedtime; lisinopril, 10 mg orally once daily; and simvastatin, 40 mg orally once daily.

Past Medical History

The patient had a history of hypertension, hypercholesterolemia, and a recently diagnosed right-sided renal cell carcinoma, which was localized and removed. She had not undergone surgery before 2002 and did not have a history of atopy. Indeed, she never reported symptoms consistent with eczema, asthma, hives, or seasonal (or perennial) allergies. Also, before her first attempted nephrectomy, the patient had never been catheterized.

Drug and Food Allergies

She had no known drug allergies and no known food allergies. She had eaten peaches and many other kinds of fruits many times before her surgery without experiencing any kind of reaction.

Family History

The patient's mother had died of pancreatic cancer and her father of a myocardial infarction; her sister was currently alive and well. No family members had a history of atopy, asthma, drug allergy, or intraoperative anaphylaxis.

Social History

The patient lived with her husband in Mexico and had smoked approximately 1 pack of cigarettes a day for 20 years before quitting 1 year ago. She drank alcohol rarely and denied illicit drug use.

Occupational Exposure History

The patient worked as a housewife and had never worked in the medical field or the rubber industry. Further, she rarely used rubber gloves to clean her house, but when she did she never remembered having a reaction to them or any other

latex product, whether this reaction be a localized rash or more systemic symptoms, such as hives, wheeze, angioedema, or pruritus.

Physical Examination

The patient appeared healthy and well nourished. Her blood pressure was 150/70 mm Hg, and her pulse was 80/min. The examination findings were unremarkable except for a well-healed nephrectomy scar.

2. What are the most likely explanations for this patient's 3 episodes of anaphylaxis?

- A. Latex allergy
- B. Latex fruit syndrome
- C. Separate allergies to muscle relaxants and peaches

This patient presented with 2 episodes of unexplained intraoperative anaphylaxis followed by a third anaphylactic episode while eating a peach. This reaction to a peach could not be well explained by a prior reaction to muscle relaxants, because there is no reported cross-reactivity between peaches and muscle relaxants. Latex allergy alone (without concomitant peach allergy) could only explain all of her symptoms if the peach to which she eventually reacted had been handled with latex gloves, a possibility that would be made less likely if the patient had tested positive to peach skin. In retrospect, this patient presented with a clinical history much more suggestive of latex fruit syndrome.

It is not certain why patients sensitized to latex should be more prone to developing food allergies or, in reverse, why patients with various food allergies should develop latex allergy, but multiple foods have now been shown to cross-react with latex, both clinically and immunologically. The most commonly implicated foods in the so-called latex fruit syndrome include avocado, kiwi, banana, and chestnut, but other cross-reactions have now been discovered, including melons, apple, potato, tomato, celery, papaya, figs, passion fruit, pineapple, hazelnut, peanut, peach, apricot, plum, and cherry.⁸⁻¹²

If this patient does indeed have the latex fruit syndrome, it appears that her latex sensitivity preceded her sensitivity to peach. The literature supports this sequence of acquired sensitivity but also offers examples where the reverse is true (a cross-reactive food sensitivity occurs before a clinically apparent latex allergy).^{13,14} It is unclear how this patient came to be sensitized to latex, and her history offers few clues. Although she may have been sensitized before her surgery by cross-reacting pollen or food, she gave no history of pollen or food allergy and did not offer a history consistent with any of the other aforementioned risk factors for latex allergy. Unfortunately, this inability to pinpoint the mechanism of sensitization is common and may or may not be partly explained by the inherent difficulty of taking an accurate latex history, especially given the widespread use of latex in common household items. There is less question about the source of the latex that caused her 2 intraoperative anaphylactic reactions. These reactions occurred after mucosal contact with

latex-containing products in the operating room, most likely, her surgeon's gloves.

The patient's subsequent reaction to a peach after displaying clinical symptoms of latex sensitivity has been shown to be a frequent occurrence. Food allergies in patients with predisposing latex allergy have been reported to be as high as 50%.⁹ On the other hand, patients with food allergies display a clinically evident latex allergy only approximately 11% of the time, a possible indication that latex sensitization is more likely to occur before the development of food allergy.¹¹ A study by Ortiz et al¹⁴ showed that of 57 fruit allergic patients, 85.9% of them had been immunologically sensitized to latex, and all of those sensitized displayed clinical symptoms of fruit allergy before latex allergy. These conflicting data regarding the order of sensitization probably argue that indeed both fruits and latex may serve as sensitizers and that the prevalence of which route is most common depends on each patient's exposure history.

Testing

Given the clinical suspicion of latex fruit syndrome, the decision was made to skin test the patient for latex and peach, along with several foods known to cross-react with latex. Skin prick testing was performed to evaluate for latex allergy with both glove and sap extract (Table 1). The latex glove extract used for diagnosis was prepared by cutting the glove into pieces and soaking them in phosphate-buffered saline at 4°C for 12 hours. The extract was then sterilized through a 0.22-μm filter before testing. The nonammoniated latex gloves were bought from VWR International Company, Mississauga, Ontario, and were shown to have a protein content of 1.8 mg/mL, whereas the sap extract was obtained from Johnson and Johnson, New Brunswick, NJ. Skin prick testing with both sap and glove extract was started at a dose of 1:1,000,000 (wt/vol) and progressed until the patient displayed a positive reaction, which was designated as a wheal 3 mm larger than the saline control (in addition to surrounding erythema). Dilutions were increased by a factor of 10 every 20 minutes until 1/100 (wt/vol) was reached. Histamine at 6 mg/mL was used as a positive control, and small pox needles were used for the latex and food skin prick testing.

Table 1. Latex Skin Prick Results for the Different Dilutions of Latex Glove and Sap Extract*

Dilution (wt/vol)	Wheal/flare, mm	
	Latex glove	Latex sap
1:1,000,000	0/0	0/0
1:1,000,000	0/0	0/0
1:10,000	0/0	0/0
1:1000	5/0	8/0
1:100	7/0	9/20

*The latex glove 1:100 (wt/vol) dilution is indeterminate given the lack of a flare reaction. The latex sap skin test result is positive, because there is surrounding erythema along with a wheal that is 3 mm greater than the negative control. The wheal/flare reactions were 0/0 mm for saline and 8/13 mm for histamine.

At a 1:100 (wt/vol) dilution, the patient displayed a positive reaction to the latex sap extract and an indeterminate reaction to the latex glove extract. At this point in the testing, the patient described mild skin and eye pruritus, so the decision was made not to advance to intradermal testing for the latex glove extract, especially since the latex sap extract was already positive. The patient's symptoms did not progress and resolved soon after she received fexofenadine, 180 mg.

On a subsequent visit, the patient was also skin tested to several foods, in addition to peach, that have been reported to cross-react with latex (Table 2). She displayed a positive reaction to fresh plum, papaya, tomato, and almond extract, but her initial skin test result was negative to a commercial peach extract. Because culprit allergens in fruit may be degraded in commercial extracts, the patient was tested with a fresh peach, the results of which were positive.^{15,16} Although chestnuts were unavailable and not tested, negative reactions were noted for fresh banana, kiwi, and avocado and also for the commercial extracts of cantaloupe, cacao, and grape.

The findings that this patient had a negative skin test result to peach extract but a positive skin test result to fresh peach support the results of previous investigations that testing with fresh food is more sensitive than commercial extracts.^{17,18} This same lack of sensitivity applies to in vitro IgE food testing, which was not performed.¹⁹ Blanco⁹ showed an 80% concordance between fruit culprits thought to be cross-reactive with latex and prick-prick testing with that same fresh food. Again, it is thought the active allergenic fruit proteins are probably degraded during commercial preparation.¹⁶ Skin testing for the muscle relaxants was not performed but would have been the next diagnostic maneuver if the latex test results had been negative.

Table 2. Commercial Extract and Fresh Fruit Skin Prick Test Results*

Substance	Result
Histamine	4+
Saline	0
Peach extract	0
Almond extract	3+
Cantaloupe extract	0
Grape extract	0
Fresh peach	4+
Fresh plum	4+
Fresh banana	0
Fresh kiwi	0
Fresh avocado	0
Fresh tomato	3+
Fresh papaya	4+

*A 4+ reaction indicates a wheal at least 3 mm greater than the negative control with pseudopods and surrounding erythema; 3+, same response but without the pseudopods; 1+ or 2+ (not applicable), not positive because they did not meet these criteria; and 0, failed to register a wheal or flare.

3. What evidence from the literature supports an immunologic link between latex and peaches and what could be the possible cross-reactive epitope(s)?

Peach, apricot, plum, nectarine, and cherry are members of the stone fruit family or the subfamily Prunoideae. This subfamily falls under the larger umbrella of the Rosaceae family, which contains more than 3,000 species of trees, herbs, and shrubs and also includes almond, pear, loquat, rose, and strawberry. The stone fruits have been shown to be clinically cross-reactive among themselves in patients with the oral allergy syndrome, likely a result of a shared 13-kDa IgE-binding component.²⁰ Whether this major allergen is responsible for cross-reaction between the stone fruits and latex is not known, but data exist to support an immunologic link between the two. Radioallergosorbent test inhibition studies performed by Weiss et al⁸ showed significant inhibition of latex specific IgE by extracts from peach, plum, and nectarine. Further studies to define the molecular basis for this inhibition have yet to be published. It has been suggested that class I chitinases may represent a panallergen that could help explain the apparent cross-reactivity between latex and so many fruits.²¹ Class I chitinases with an N-terminal hevein-like domain are homologous to latex hevein (Hev b 6.02), a major IgE-binding allergen for patients allergic to latex.²² However, this does not clearly explain the present patient's reaction to peach and not the more commonly cross-reactive foods such as avocado, banana, and kiwi. This unique cross-reactivity with the stone fruits, to the exclusion of other commonly cross-reactive foods, may argue for an alternate immunologic explanation. Evidence would seem to point toward an undiscovered common epitope between latex and the stone fruits.

Rosaceae fruits, primarily peach, are one of the most common causes of food-induced anaphylaxis in the Mediterranean. Lipid transfer proteins (LTPs) are thought to represent the primary allergen among these Rosaceae fruits in this region of the world.^{23,24} The amino acid sequences of the LTPs are highly conserved among the different members of the Prunoideae family and explain the significant clinical cross-reactivity among apricots, peaches, plums, and cherries.²⁵ These LTPs are found in the highest concentration within the peels (rather than the pulps) of these fruits and may cause severe food reactions because of their resistance to pepsin digestion.^{23,26,27} Although it is not yet known if these LTPs may be homologous to latex allergens, the LTP known as Pru p 3 has recently been shown to be the major peach allergen in the Mediterranean area.²⁸

The varying severity of reactions to Rosaceae fruits, from oral allergy to anaphylaxis, may be explained by the presence of 2 or more different allergenic proteins. The previously mentioned 13-kDa IgE-binding component that may be responsible for stone fruit cross-reactivity among patients with oral allergy syndrome is different from the LTP that has been shown to be responsible for systemic reactions in the Mediterranean population. Further, birch pollen, via Bet v 1, is known to sensitize patients only to the culprit protein (pos-

sibly the 13-kDa IgE-binding component) responsible for oral allergy syndrome, not to LTPs.²⁵ Systemic reactions in patients with oral allergy syndrome may therefore be caused by separate and unique protein allergens. Because of our patient's systemic reaction to peach, it would be unlikely that she would be sensitized to a protein responsible for oral allergy syndrome and more likely that she would be sensitized to a more resistant protein like an LTP such as Pru p 3.

Treatment

Appropriate management of a patient with the latex fruit syndrome includes education about commonly associated cross-reactive foods. Given the numerous foods that have been shown to be cross-reactive with latex, it would prove too nutritionally restrictive to recommend avoiding all of them.²⁹ In our patient's case, we recommended avoidance of all stone fruits, including plums and the obvious culprit peach, to which she was skin test positive. We also urged her to avoid almonds (another member of the Prunoideae subfamily) and papayas, both of which have been shown to be cross-reactive with latex and both to which she tested positive. We did not recommend that she avoid cooked or uncooked tomatoes, since she had eaten both without incident after her reaction to peach. If she wanted to eat a cross-reactive food that she had not tried before and for which we did not skin test, we recommended that she first return to her allergist for both a skin test and, if the result was negative, a monitored challenge. In addition to education about cross-reactive foods, we explained the importance of latex avoidance both in and out of surgery. The patient was given a brochure that contained a list of latex-containing products and training on how to use injectable epinephrine (EpiPen) in case of a future life-threatening reaction. She was also given a Medic-Alert bracelet.

Although the staple treatment of latex allergy is clearly avoidance, attempts have been made to treat patients with latex-specific immunotherapy. Clinical benefits have been achieved, with noted improvements in rhinitis, conjunctivitis, and cutaneous symptoms; however, the relatively high incidence of systemic reactions that have occurred during latex immunotherapy (compared with aeroallergen immunotherapy) so far precludes this option.³⁰

CONCLUSION

This patient emphasizes the importance of an empiric suspicion of latex allergy as a cause of intraoperative anaphylaxis. Although this patient's subsequent reaction to a peach helped make the diagnosis clear, an initial referral for latex testing or, at the least, an initiation of latex precautions before the second surgery may have helped avoid further reactions. Given the significant prevalence of latex as a cause for intraoperative anaphylaxis (12% to 16%), it would seem prudent to consider it in all cases such as this.

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